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Original article:

A Prospective study on the Incidence of Post Transplant Diabetes Mellitus (PTDM) at 6 months post renal transplantation and Assessing the utility of Capillary Blood Glucose(CBG) monitoring for diagnosis of PTDM

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Abstract

Introduction: Post Transplant Diabetes Mellitus (PTDM) is the de novo occurrence of Diabetes mellitus after a solid organ transplant. The reported incidence of PTDM ranges from 4-25%. Based on International Consensus Guidelines-2014, the diagnosis of PTDM is made using the American Diabetes Association (ADA) criteria.

Aim: To study the incidence of PTDM at 6 months post renal transplantation and assess the utility of Capillary Blood Glucose (CBG) monitoring in the diagnosis of PTDM.

Methodology: 30 consecutive renal transplant recipients above the age of 18 years were inducted into the study and followed up for a period of six months after renal transplant. At discharge, patients were advised on monitoring of CBG at specified time points (Fasting, Post-lunch, Post dinner), at home using a Glucometer. Oral glucose tolerance test (OGTT) was done at months 1, 3 and 6 post renal transplant in patients not diagnosed with PTDM by Home monitoring of blood glucose.

Results: The incidence of PTDM at 6 months after renal transplantation was 36.6% in our study. PTDM was diagnosed in 6 , 3 and 2 of the patients at month 1, month 3 and month 6 post-transplant, respectively. In those who developed PTDM, blood glucose levels showed a characteristic pattern of post prandial glycemic excursions with fasting euglycemia.

Conclusion: Most diagnosis of PTDM is made in the early post transplant period with a higher incidence in people of Asian ethnicity. Diagnosis of PTDM was established in two thirds of the patients by Capillary blood glucose monitoring.

Introduction

Solid organ transplantation (SOT) is associated with glucose intolerance and *de novo* development of diabetes mellitus post- transplant (1,2) generally referred to as Post Transplant Diabetes Mellitus (PTDM). Abnormalities in insulin secretion and insulin sensitivity coupled with use of immunosuppressive medications which are diabetogenic are central to the development of PTDM (3). It is a major co-morbidity that has significant impact on the patient and allograft outcome. The reported incidence of PTDM is variable and ranges from 4-25% (4). Historically, it was defined variedly based on random and fasting glucose values or the use of insulin or oral hypoglycemic agents in the post transplant period. In order to ensure uniformity in diagnosis and reporting, a consensus guideline was formulated and PTDM was defined according to the American Diabetes Association criteria. The guidelines

recommend screening all kidney transplant recipients with fasting plasma glucose (FPG), Oral Glucose Tolerance Test (OGTT), and/or glycated haemoglobin (HbA1C) assay at least weekly for 4 weeks, every 3 months for 1 year, and annually thereafter (5). Though OGTT is the gold standard diagnostic test for PTDM, it has not been used routinely due to cost constraints. Diagnosis of PTDM using HbA1c in the early post transplant period has not been fully validated since the results may be affected by systemic illness or ongoing graft dysfunction or anemia. Home based self monitoring of blood glucose has been encouraged for people with diagnosed PTDM and pre-transplant diabetes mellitus. This prospective study was designed to evaluate the incidence of PTDM in a cohort of renal transplant recipients and assess the utility of Capillary Blood Glucose (CBG) monitoring for early detection of hyperglycemia and confirm the diagnosis of PTDM.

Aim

To study the incidence of Post Transplant Diabetes Mellitus (PTDM) at 6 months post renal transplantation and to study the occurrence of hyperglycemia by monitoring Capillary Blood Glucose (CBG) levels at specified time points.

Methodology

The prospective observational study was conducted in the department of Nephrology at Narayana Hrudayalaya Hospitals, Bengaluru. After IEC clearance and informed consent, 30 consecutive renal transplant recipients above age of 18 years, were recruited into the study. All of them were followed up for a period of 6 months post renal transplant. Patients with diagnosis of diabetic kidney disease or who were on anti-diabetic medicines any time pre-transplant were excluded from the study. Details of age, gender, modality of dialysis , native kidney disease, dialysis vintage, family history of diabetes, HCV serology status, BMI, degree of HLA mismatch and type of induction agent used were obtained. Other pre-transplant investigations and the general post- transplant care were as per the standard of care. All patients were followed up for a period of 6 month after transplantation. In the early post operative period, Blood glucose evaluation at specified time points (Fasting, Post-lunch(PL), Post-dinner(PD)) was done till the time of discharge . At discharge, patients were advised on Home based Self monitoring of blood glucose levels at specified time points (Fasting, Post-breakfast(PB), Post-lunch and Post-dinner glucose levels) using a Glucometer, which the patients checked thrice a week in the first month and once a week in the next 5 month. Oral glucose tolerance test (OGTT) was done at months 1, 3 and 6 post renal transplant in patients not diagnosed with PTDM by Capillary blood glucose monitoring. The various time point of diagnosis of PTDM was recorded and those diagnosed with PTDM were managed by the primary physician/endocrinologist.

Definition of endpoints-

1. Post transplant diabetes mellitus is defined as per the ADA Criteria(Appendix I) **&** by Home based glucometer Capillary blood glucose (CBG) values with more than two post meal readings above 200mg/dl. A formal diagnosis of PTDM was made on follow up when patients had stable renal allograft function on maintenance immunosuppression in the absence of acute infections.

2. Post-transplant transient hyperglycemia is defined as hyperglycemia that can occur upto Day 45 post kidney transplant due to immunosuppression and infections. For the sake of this study, we assumed all patients who qualify for the diagnosis of impaired blood sugars as PTDM regardless of the onset of their dysglycemia. In the final analysis those patients who were diagnosed with PTDM in the first 45 days, but have been maintaining normal glucose levels without medications subsequently were re-assessed and formal OGTT performed in these patients to clarify their glycemic status.

Statistical Methods:

Microsoft Excel was used for compiling patient's baseline data. Statistical Software-SPSS version 17.0 was used for descriptive and inferential data analysis. Results on continuous variables are presented on Mean±SD and results on categorical variables are presented in number as percent (%). Correlation between categorical variables was done using Fisher's exact test. Correlation between continuous variables was done using Mann-Whitney test. *p* value of <0.05 was considered statistically significant.

The incidence of PTDM is presented as percentage of the transplant cohort at the end of 6 months. Univariate analysis was performed to determine the significant risk factors associated with development of PTDM. However, a multivariate analysis to determine the impact of various independent risk factors was not feasible due to the small sample size of the study.

Results

Of the 30 subjects, 28 patients underwent live related kidney transplant and 2 patients underwent deceased donor kidney transplant. Male patients constituted majority of the subjects, with the male to female ratio of 4:1. Patient's age ranged from 17 years to 53 years with a mean age of 36.5±9.9 years. The native kidney disease was a mix of various causes of ESRD. Pre-transplant fasting blood glucose and 2 hour post-prandial glucose were normal with a mean value of 87.1 mg/dl and 110.7 mg/dl respectively. The demographic data of all the 30 subjects of the study are given in Table 1.

Table 1. Demographic details of all the renal transplant patients

Parameter	**n = 30**	**Per cent (%)**
Age (years)		
<30	8	26.7
30-40	10	33.3
>40	12	40
Sex		
Male	24	80
Female	6	20
Native kidney disease		
ADPKD	1	3.3
CGN	23	76.7
IgA Nephropathy	2	6.7
Post-partum cortical necrosis	1	3.3
Renal calculi disease	1	3.3
Obstructive uropathy	1	3.3
Type of Dialysis		
Haemodialysis	28	93.3
Peritoneal dialysis	1	3.3
Pre-emptive transplant	1	3.3

The incidence of PTDM at six months post renal transplantation was 36 % in our study, as shown in Table 2. Of the 30 subjects, PTDM occurred in 11(36%) subjects. Post-transplant transient hyperglycemia (PTTH) was found in 17 (56%) of the patients. Out of the 17 patients with PTTH, 11 patients developed PTDM while 6 patients became euglycemic at the end of 6 months follow up period.

Table 2. Incidence of PTDM and PTTH in the study

PTDM			**PTTH**		
	Frequency	Percent (%)		Frequency	Percent (%)
Y	11	36.7	Y	17	56.7
N	19	63.3	N	13	43.3
Total	30	100.0	Total	30	100.0

During the first month of follow-up, weekly mean FBS was below 100 mg/dl. The average values of PB, PL, PD blood glucose was between 130mg/dl, 170 mg/dl and 150 mg/dl respectively. Subsequently, over the next five months, the mean FBS values remained below 100 mg/dl and the mean values of PB, PL,PD blood glucose were 125mg/dl, 165 mg/dl and 150mg/dl respectively. During the six month follow-up, the mean PL blood glucose values remained consistently high. The highest PL blood glucose values were seen during week 3, week 4, month 1 and month 3. The trend of blood glucose values at various time points are depicted in the Figure 1& 2.

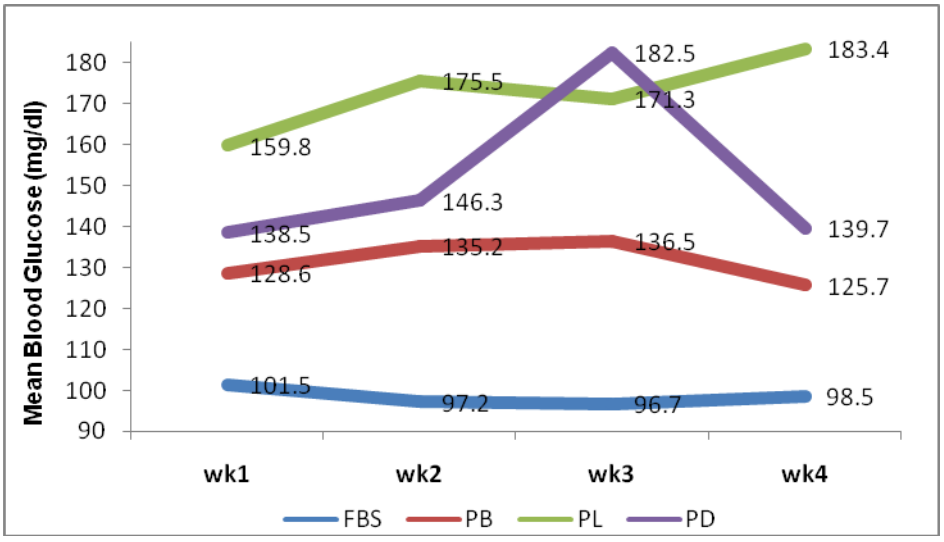

Figure 1. Trend of weekly blood glucose levels during the first month post-transplant

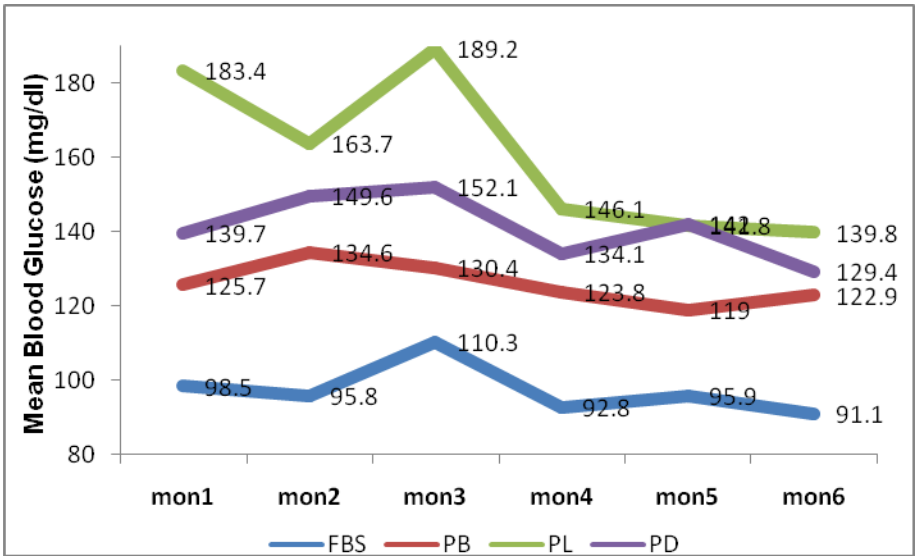

Figure 2. Trend of monthly blood glucose levels between first and six month post-transplant

Though OGTT was used as the diagnostic test for PTDM, a good number of patients were diagnosed with overt diabetes by the capillary blood glucose testing. During the home glucometer monitoring, significant number of patients were found to have fasting and post lunch blood glucose levels in the range between 130-180mg/dl and 250- 400 mg/dl respectively. Blood glucose values of subjects diagnosed with PTDM using Capillary blood glucose levels and OGTT are shown in Figure 3 and 4 respectively. The percentage of subjects diagnosed with PTDM using either of the method is shown in Table 3.

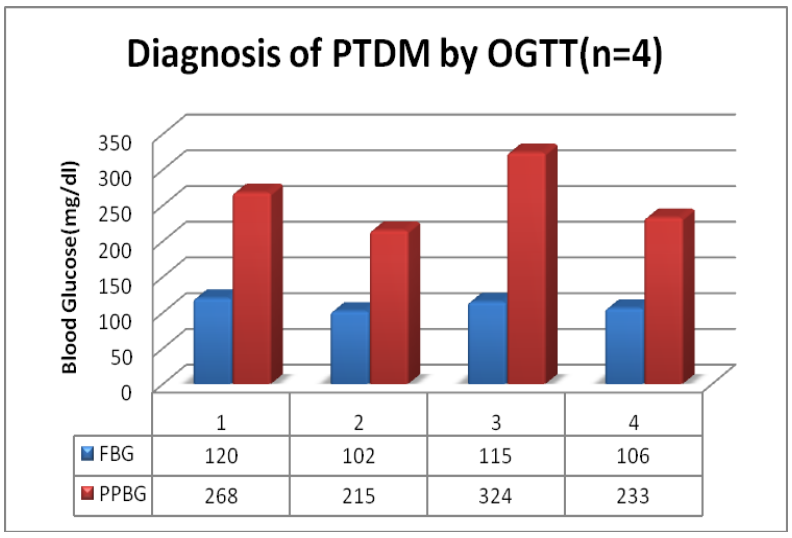

Figure 3. Fasting and Post prandial Blood glucose levels at diagnosis of PTDM by OGTT(n=4)

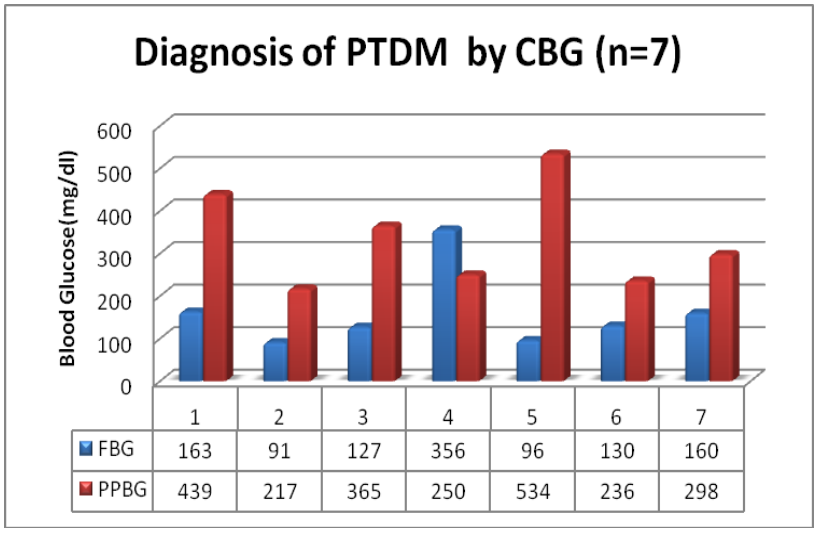

Figure 4. Fasting and Post prandial Blood glucose levels at diagnosis of PTDM by Capillary Blood Glucose(CBG) monitoring (n=7)

Table 3. Number of subjects diagnosed PTDM by OGTT v/s Home Glucometer monitoring

Diagnostic method	**n=11**	**Percent (%)**
OGTT	4	36.4
Home Glucometer monitoring	7	63.6

In our study, during the six month follow-up period, the cumulative incidence of PTDM was 20% at first month, 30% at third month and 36.6% at sixth month post-transplant. In the study population, PTDM was diagnosed in 6, 3 and 2 of the patients at month 1, month 3 and month 6 post-transplant, respectively.

Discussion

In our study the incidence of PTDM was 36.7% at six most after renal transplantation. Globally, the reported incidence of PTDM ranges from 4-25% (4). Based on the US database of renal transplant recipients, it was reported that the cumulative incidence of PTDM was 9.1% at 3 months, 16% at 12 months, and 24% at 36 months (6). Other studies on Cauacsian population show the incidence of PTDM between 7-18 % (7,8). Among the Indian studies and other studies on people of Asian ethnicity, a higher incidence ranging from 20-33% was reported (9,10,11,12). Most data on the incidence of PTDM comes from retrospective studies. Also, most studies reporting PTDM lacked uniformity in the definition of diabetes mellitus, screening protocols and follow up period. Since the incorporation of the consensus definition on PTDM given in the year 2014, the reported incidence seems to be higher, thus showing that PTDM was an under diagnosed entity till then. We found an overall higher incidence of PTDM in our cohort, as compared to the previous reported incidence estimates of Indian retrospective data.

Post transplant transient hyperglycemia (PTTH) is a recently introduced terminology during the consensus meeting on PTDM in 2014. In our study, all the patients who developed PTDM had Post Transplant

Transient Hyperglycemia (PTTH). In our study we found 56% of patients to have had PTTH. In those who developed PTDM, all the patients had PTTH. In those who did not develop PTDM, 36% patients had PTTH. Presence of PTTH was found to have significant association with occurrence of PTDM ($p< 0.004$). Our study results correlate very well with previous studies (13,14) where in-patient and early hyperglycemia post-transplant prove to be a major risk factor for future PTDM. With the new definition of PTTH in place, studies with new design and testing strategies in high-risk patients may be the next logical step in prevention of PTDM.

Recognizing the fact that early hyperglycemia post-transplant is a strong predictor of future PTDM, we monitored the trend of blood glucose levels at specified time points. A study by Sommanavar et al has shown that Random Capillary Blood Glucose (RCBG) estimation closely relates to 2 hr post prandial blood glucose values (12). Measurement of CBG has an advantage that it can be undertaken at any time of the day, does not require a venipuncture and can even be performed by laypeople and cuts the cost of screening. They recommend CBG as an effective screening tool and those individuals with CBG >110mg/dl should undergo definitive tests for diagnosis of diabetes mellitus. Based on the study by Sommananvar et al (15), we considered capillary blood glucose estimation by glucometer as a convenient and accurate option to detect hyperglycemias. To our knowledge, we know of only one study by Amish Shah et al (16) who conducted a study in 2005 using home glucometer monitoring for blood glucose for early diagnosis of PTDM in 117 renal transplant recipients. A diagnosis of PTDM then was being considered based on “a new requirement for insulin therapy for more than 30 days” or “a new requirement for insulin or oral hypoglycemic agents”. In their study, 28 (31%) patients were diagnosed with PTDM. Of them 19 (60%) patients were diagnosed by home glucometer showing blood glucose values beyond 200 mg / dl at pre-lunch and pre-dinner. The remaining 5 (18%) patients were diagnosed by plasma glucose values at clinic visits. They concluded that, home glucometer monitoring markedly improved the diagnosis of PTDM and recommended further studies to measure post prandial glucose values as a better marker of glycemic control.

More than a decade later, our study using post prandial (breakfast, lunch and dinner) blood glucose values showed similar results in the diagnosis of PTDM. In our study, we recognized a pattern of capillary blood glucose values. In the entire cohort we found fasting values to be within the normal range. The post-prandial, specifically post- lunch and post- dinner values showed a rising trend. Through the weekly monitoring in the first month post transplant, the post-lunch and post-dinner glucose values peaked during the third and fourth weeks. Subsequent monitoring over the six month showed a similar pattern of peaking post prandial values while the fasting glucose values were in the normal range. When we looked at the trend in those who developed PTDM, much to our expectation, the post prandial (lunch and dinner) glucose values were significantly higher. Of the 11 (36%) patients with PTDM, 7 (63%) met ADA criteria for diabetes mellitus based on home glucometer monitoring. All diagnoses were made based on post-lunch or post-dinner glucose values of more than 200 mg/dl. Additionally, the pattern of post prandial hyperglycaemia with fasting euglycemia was observed in all our patients who developed PTDM. Adding evidence to the above study, our observations seem to be highly relevant in establishing a diagnosis of PTDM by home glucometer monitoring of blood glucose. The remaining 4(36%) patients were diagnosed PTDM by a formal Oral glucose Tolerance Test (OGTT) done during the six month follow-up period. The possible explanations for the characteristic glycemic pattern is the effect of medications like steroids and tacrolimus taken in the daytime, which are known to have a bearing on the insulin resistance and insulin secretion in response to a carbohydrate load. This pattern of PTDM occurring in the first few months post-transplant is in keeping with the initial use of higher doses of steroids and the treatment of early rejection

episodes. Across the population types, the development of PTDM seems to occur mostly within the first 6 months post- transplant. In our study, during the six month follow-up period, the cumulative incidence of PTDM was 20% at first month, 30% at third month and 36.6% at sixth month post-transplant. Our study along with other reports confirms that incidence is higher in the initial post-transplant period. The prospective study design and inclusion of PTTH as a well defined entity remain the major strengths of the study. However, we consider the sample size and short follow up period as limitations of the study.

Conclusions

The incidence of Post Transplant Diabetes Mellitus (PTDM) in our cohort of renal transplant recipients was 36.6%. Most diagnosis of PTDM is made in the early post transplant period. Post-transplant, blood glucose levels show a characteristic pattern of post prandial glycemic excursions with fasting euglycemia in those who develop PTDM. Of the patients with PTDM, two thirds were diagnosed based on monitoring of Capillary blood glucose with post prandial values above 200 mg/dl. We strongly recommend adopting Home monitoring of blood glucose as a part of routine post transplant care. This appears to be a convenient and accurate method to diagnose PTDM early in the post transplant period, thus overcoming the inconvenience associated with frequent clinic visits and expensive testing.

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